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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/747,798
Filing Date: December 29, 2003
Appellant(s): YOO, GEORGE H.

Monica A. De La Paz
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 23 August 2006 appealing from the Office action mailed 14 April 2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

2001/0044420	Nielsen et al.	11-2001
WO 99/66946	El-Deiry et al.	12-1999
WO 00/29024	Zhang et al.	05-2000

Clayman, G. "Clinical protocol for wild type p53 gene induction in premalignancies of squamous epithelium of the oral cavity via an adenoviral vector" PowerPoint presentation, March 2001.

Oda et al. "Chromosomal abnormalities in HPV-16-immortalized oral epithelial cells" Carcinogenesis, vol. 17, no. 9, (1996), pp. 2003-2008.

Flaitz et al. "Molecular piracy: the viral link to carcinogenesis" Oral Oncol. vol. 34 (1998), pp. 448-453

Recombinant DNA Advisory Committee, Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services.

Kaghad et al. "Monoallelically expressed gene related to p53 at 1p36, a region frequently deleted in neuroblastoma and other human cancers" Cell, vol. 90 (1997), pp. 809-819.

Hay, D. "Management of oral problems associated with cancer treatment: radiotherapy", www.8.co.nz/hospitaldentistry/papers/Management_of_Oral_Problems_Associated_with_005.htm, accessed by PTO on 10/11/06.

Lowe, B. "Abnormal Cervical Smears - a patient's guide" www.medic8.com/healthguide/articles/abnormalcervicalsmear.html, accessed by PTO on 10/11/06.

"What is a dermatologist?" www.aad.org/public/Parentskids/KidsConnection/Whatisderm.htm, accessed by PTO on 10/11/06.

Examiner note:

The reliance on the Hay, Lowe, and "What is a dermatologist?" documents was necessitated by unsubstantiated assertions made by Appellant for the first time in the brief in sections VII.A.2.; VII.B.2.; and VII.C.2. Thus, their use in this Examiner's Answer (section (10) below under *Response to Brief sections VII.A.2.; VII.B.2.; and VII.C.2.*) does not constitute new grounds of rejection.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 stand rejected under 35 U.S.C. 102(a) as being anticipated by Clayman, G., Ref. C95 of the IDS filed 8/16/04, as evidenced by Oda et al. (Carcinogenesis 17(9): 2003-2008, 1996) and Flaitz et al. (Oral Oncol. 34: 448-453, 1998), and as evidenced by Recombinant DNA Advisory Committee (RAC), Minutes of Meeting March 8, 2001, U.S. Dept. of health and Human Services, for the reasons of record set forth in the Office action of 11/17/05, which are repeated below.

Clayman describes a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector (see pages 4-6 especially).

Clayman does not mention papilloma virus infection of cells in the lesion, however, this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment. Oda discloses that up to 90% of oral cancers have been reported to contain HPV DNA (p. 2003, col. 2), and Flaitz discloses that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Consequently, one of skill in the art of oral cancer would have been aware that the treatment of Clayman would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells in a substantial fraction of target patients. With respect to the limitation that the composition be formulated as a douche solution (e.g. claims 18, 33, 54), a douche is simply a jet of liquid applied to a part of the body; so a douche solution is simply liquid.

Claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 stand rejected under 35 U.S.C. 102(b) as being anticipated by Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12), as evidenced by Oda et al. (Carcinogenesis 17(9): 2003-2008, 1996) and Flaitz et al. (Oral Oncol. 34: 448-453, 1998), for the reasons of record set forth in the Office action of 11/17/05, which are repeated below.

Clayman, G., Ref. C23 of the IDS filed 8/16/04 appears in the on-line Recombinant DNA Advisory Committee publication at pages 10-11.

Recombinant DNA Advisory Committee (RAC) describes a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector (see pages 10-11 especially).

RAC does not mention papilloma virus infection of cells in the lesion, however, this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment. Oda discloses that up to 90% of oral cancers have been reported to contain HPV DNA (p. 2003, col. 2), and Flaitz discloses that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Consequently, one of skill in the art of oral cancer would have been aware that the treatment of Clayman described in RAC would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells. With respect to the limitation that the composition be formulated as a douche solution (e.g. claims 18, 33, 54), a douche is simply a jet of liquid applied to a part of the body; so a douche solution is simply liquid.

Claims 1-14, 19-29, 38-50, and 55-60 stand rejected under 35 U.S.C. 102(b) as being anticipated by Nielsen et al., US 2001/0044420, as evidenced by Oda et al. (Carcinogenesis 17(9): 2003-2008, 1996) and Flaitz et al. (Oral Oncol. 34: 448-453, 1998) with respect to claims

1-14, 19-29, 38-50, 55-60, for the reasons of record set forth in the Office action of 11/17/05, which are repeated below.

Nielsen describes the treatment of cancer in general, including cervical cancer and head and neck cancer, by a combination of p53 gene therapy and gemcitabine chemotherapy. The p53 gene can be delivered by non-viral lipid-based plasmid delivery or by delivery in a viral vector based on adenovirus, AAV, retrovirus, or vaccinia virus. The p53 coding sequence in the vector may be under control of a constitutive or tumor specific promoter. Nielsen discloses topical delivery of the vector to the location of a tumor, including to the surgical wound resulting from tumor resection. Pharmaceutical compositions comprising the vector include compositions for transmucosal or transdermal delivery for treatment of tumors in the mouth, nasal mucosa, vagina and uterus are disclosed. Disclosed compositions include emulsions (i.e. cream, ointment or salve), aerosols, tablets, lozenges and suppositories. See entire document, especially paragraphs 0003-0006, 0009, 0013-0016, 0022, 0029, 0038, 0064, 0076, 0083, 0088-0093, and 0101-0104, and claims 1-10, 34-35.

Nielsen does not mention papilloma virus infection of cells in the lesion, however, this characteristic is inherent in a substantial fraction of patients that would be the target of the disclosed treatment where the cancer is head and neck or cervical cancer. Oda discloses that up to 85-90% of cervical cancers have been reported to contain HPV DNA (p. 2003, col. 2), and Flaitz discloses that about 50% of oral epithelial dysplasias are infected with HPV, and between one-third to one-half of oral squamous cell carcinoma involve HPV infection (page 452). Consequently, one of skill in the art of oral cancer would have been aware that the treatment of Nielsen would necessarily involve treatment of hyperplastic lesions that comprise HPV infected

cells when treating head and neck or cervical cancer in a substantial fraction of target patients. With respect to timed-release formulations, formulations such as creams, ointments, tablets, suppositories, etc. release their contents as the carriers break down over time, and so are timed-release.

Claims 1-15, 18-29, 33, 38-51, 54-60 stand rejected under 35 U.S.C. 102(b) as being anticipated by El-Deiry et al., WO 99/66946, for the reasons of record set forth in the Office action of 11/17/05, which are repeated below.

The instant specification (page 14, lines 5-10) states: "the term "p53" is intended to refer to the exemplified p53 molecules as well as all p53 homologues from other species". The invention of El-Deiry relates to gene therapy with a transgene encoding p73, a homolog of p53 (El-Deiry, Abstract, page, 12, lines 32-33, and page 22, line 26, to page 23, line 23). Given the definition of "p53" in the instant specification, p73 is embraced by the term "p53" recited in the instant claims.

El-Deiry discloses the treatment of cells transformed by infection with a papilloma virus, such as HPV, particularly those in certain types of cancer involving papilloma virus infection, e.g. cervical cancer, esophageal squamous cell cancer, laryngeal papilloma, bronchio-alveolar carcinoma, penile carcinoma and bladder carcinoma. El-Deiry teaches methods of treating such cells *in vivo* by gene therapy with a vector that expresses p73, including by topical delivery. The vector may be a liposomal vector or a viral vector based on a retrovirus, adenovirus, and AAV. The p73 coding sequence is under control of a constitutive promoter or papilloma virus-regulated promoter. The pharmaceutical composition comprising the vector may also include a

chemotherapeutic agent, and can be formulated as an aerosol for inhalation, in a lotion or suppository, in a liquid for oral delivery, or in a transdermal patch, and used such that the composition contacts the target cells. See entire document, especially page 1, lines 8-12 and 20-22; page 3, line 10, to page 5, line 7; pages 12-16; pages 20-23; page 24, line 33 to page 25, line 31. With respect to timed-release formulations, formulations such as creams, ointments, tablets, suppositories, etc. release their contents as the carriers break down over time, and so are timed-release.

Claims 16, 17, 31, 32, 52, and 53 stand rejected under 35 U.S.C. 103(a) as being unpatentable over either Recombinant DNA Advisory Committee (Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services, pages 10-12), as evidenced by Oda et al. (Carcinogenesis 17(9): 2003-2008, 1996) and Flaitz et al. (Oral Oncol. 34: 448-453, 1998), as applied to claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 above, or El-Deiry et al., WO 99/66946, as applied to claims 1-15, 18-29, 33, 38-51, 54-60 above; and further in view of Zhang et al., WO 00/29024, which are repeated below.

Recombinant DNA Advisory Committee (RAC), Oda et al., and Flaitz et al., and El-Deiry et al. are described above. RAC and El-Deiry et al. both describe liquid compositions for oral delivery of the vector, but neither describe inclusion of a flavorant in the composition.

However, Zhang et al. generally describes pharmaceutical compositions for gene therapy comprising an adenoviral vector, and teaches (pages 56-57) that compositions for oral delivery may include flavorants.

Therefore, it would have been obvious to one of ordinary skill in the gene therapy art at the time the instant invention was made to include a flavorant, such as peppermint or wintergreen oil, in a mouthwash containing the vector. The inclusion of flavorants in oral pharmaceutical compositions is routinely done to improve the palatability of the composition.

(10) Response to Argument

Response to Brief sections VII.A.1.; VII.B.1.; and VII.C.1.

Appellant argues that Clayman, RAC, or Nielsen, as evidenced by Oda et al. and Flaitz et al. do not inherently teach that their respective methods involve treatment of HPV infected cells, because not all premalignancies and cancers of oral squamous epithelium or all cervical cancers are associated with HPV infection, and therefore there is only the possibility or probability that treating cancers as taught by Clayman, RAC, or Nielsen would involve treating HPV infected cells, and thus, this is not inherency as viewed by the courts, e.g. *MEHL/Biophile Int'l Corp. v. Milgraum.*

In response, Appellant does not dispute that a large fraction of oral cancers (90% according to Oda et al. and 42% according to Flaitz et al.) and cervical cancers (85-90% according to Oda et al.) involve HPV infected cells, i.e. HPV infection in these cancers was recognized in this art as a causative factor. Indeed, Clayman (page 8) indicates that before treatment with the adenovirus, biopsies of the premalignancy are tested for the presence of HPV, which would indicate that Clayman was aware of the frequent involvement of HPV in oral dysplasia, as described in Oda and Flaitz.

Rather, Appellant is arguing that because there is only a possibility that the cancer of any one patient in need of such treatment would involve HPV infection, these prior art methods do not inherently anticipate the claimed method. This is a misleading analysis of the situation. One does not treat just one patient and then no others. If one uses the cited prior art methods to treat the patients for which the methods were developed, i.e. those with squamous cell premalignancies or cervical cancers, the premalignancy or cancer in at least half or most of such patients would necessarily be made up of HPV infected cells, and one would be practicing an embodiment of the claimed method. The probability only applies to what fraction of the patients being treated would involve practice of the claimed method. To put this situation a practical light, if the PTO were to grant a patent to these claims, Appellant could bar those of skill in the art from practicing the cited prior art methods on half or most of the patients for which the methods were designed and developed. This outcome is not tenable under §102.

Response to Brief sections VII.A.2.; VII.B.2.; and VII.C.2.

Appellant argues for the first time in the brief that the cited prior art does not teach the cells being treated are keratinocytes. Appellant asserts that most of the oral cavity (and presumably cervical mucosa) is lined by nonkeratinized squamous epithelium not keratinocytes.

In response, squamous cells are keratinocytes, and HPV is trophic for squamous cells and is capable of replication only in squamous cells. (See Flaitz, page 452, col. 1). Consequently, when one is treating oral or cervical cancers with the prior art methods one is treating keratinocytes.

Appellant argues for the first time in the brief that the cited prior art does not teach the cells being treated are skin cells. Appellant asserts that the oral cavity (and presumably the cervix) is not lined by skin cells.

In response, for examination claim terms, e.g. "skin", are given their broadest reasonable meaning. The mucosa of the mouth and cervix are considered to be a type of skin. See marked passages of Hay (first sheet); Lowe (first sheet); and "What is a Dermatologist? (third sheet). Consequently, when one is treating oral or cervical cancers with the prior art methods one is treating skin cells.

Appellant argues that Clayman and RAC do not anticipate "formulated as a douche solution" in claim 18; "douche solution ... comprising ... a liquid carrier formulated for vaginal delivery" in claim 33; and "formulated as a douche solution for vaginal delivery" in claim 54, because Clayman and RAC do not disclose a "jet of liquid" (i.e. a douche) or vaginal delivery.

In response, claims 18 and 54 do not require that the composition be used as a douche, only that it be formulated as a douche, i.e. these are limitations on the composition, not the steps performed with the composition. Since a douche is a liquid that can be squirted onto a body part, and the liquid composition of Clayman and RAC have that characteristic and must be mild enough not to inactivate the adenovirus, their compositions meet the limitation of claims 18 and 54. Similarly, claim 33 is directed to such a liquid, not to a method of using same, and the limitations "douche solution" and "liquid carrier formulated for vaginal delivery" are limitations of intended use, which do not materially distinguish the claimed subject matter from the composition of Clayman and RAC. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to

patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Similar to claim 18, claim 54 does not require that the composition be used as a douche or for vaginal delivery, only that the composition has the same properties as a douche formulated for vaginal delivery. Appellant has not disputed that the solution of Clayman and RAC could be used as a douche, e.g. in the mouth, or that it would be suitable for vaginal delivery as a douche. Nor has Appellant pointed to any teaching in the specification or the prior art where there would be a material difference between the simple solution containing Ad-p53 used by Clayman and RAC as a mouth rinse and a solution of Ad-p53 used as a vaginal douche. Presumably one would not use a flavorant in a vaginal douche in this context, but there is no indication that the compositions of Clayman and RAC contained a flavorant.

With respect to claims 18, 33, and 54, the heading for section VII.C.2. indicates that Nielsen does not disclose the limitations of claims 4, 6, 18, 33, and 54. Claims 18, 33, and 54 were not rejected over Nielsen.

Response to Brief section VII.D.1

Appellant argues that p53 "homologue" as it is used in the instant specification refers to the closest homologues of human p53 found in other species, i.e. the p53 itself of other species, and that p73 is not a homologue of p53. Appellant provides an opinion declaration under 37 CFR 1.132 by Dr. Zumstein as evidence to support their arguments.

In response, genes of two species that are the most structurally similar to one another in the genome of either species and have evolved from a common ancestor by speciation are termed orthologues in the art. Usually, orthologues fulfill the same biological role in both species, e.g.

human and mouse p53 genes. Another type of homologue is a paralogue. Paralogues are genes that share structurally similarity but are related to one another by duplication of a common ancestral gene. Paralogues, may or may not be functionally similar, and usually do not fulfill the same biological function, e.g. p53 and p73. Both orthologues and paralogues are homologues, i.e. they share structural similarity through common ancestry in evolution.

When an application contains a definition for a claim term, the defined meaning of that term controls over the plain meaning of the term, and the claims must be examined using that meaning assigned by the specification; see MPEP 2111.01.III and 2173.05(a). The specification at page 14, lines 5-10, states: "[T]hroughout this application, the term "p53" is intended to refer to the exemplified p53 molecules as well as all p53 homologues from other species" (emphasis added). It does not mention "human p53," nor has Appellant indicated where the specification clearly teaches that the "exemplified p53" referred to here is human p53.

Appellant contends, and Dr. Zumstein has declared, that p73 was not considered by one of skill in the art to be a homologue of p53, despite the fact that El-Deiry explicitly teaches that p73 is a homologue of p53. Further evidence that one of skill in the art clearly considered p73 and p53 to be homologues is provided in Kaghad et al., Cell 90: 809-819, 1997 (see entire document, especially page 810), contrary to Dr. Zumstein's opinion.

Appellant asserts, without supporting evidence, that the Ad vector described in the specification, i.e. Ad5CMV-*p53*, includes a sequence encoding the human p53. Even if true, this does not affect or negate the grounds of rejection. The specification does not say that the homologues are limited to p53 orthologues, nor does it exclude paralogues, such as p73. It teaches "all p53 homologues," with the possible exception of paralogues of p53 from the same

species as the "exemplified" p53, which the specification does not clearly identify. In the examples, the specification does not explicitly disclose that the p53 being expressed by the disclosed adenoviral vector is human p53. Consequently, one reading the specification may only speculate that the "exemplified p53" might mean human p53.

Had the specification clearly taught that p53 meant human p53 and p53 from other species, one of skill would have interpreted the term p53 to mean only orthologues of p53 from any species, as Appellant contends. However, that is not what the specification teaches. Instead, it teaches that p53 includes "all p53 homologues from other species," which one of skill in the art would interpret in its broadest reasonable sense to mean any p53 homologue of any type - both orthologues and paralogues, i.e. "p53" as defined in the specification would include the p53-paralogue p73. If, as Appellant asserts, the "exemplified" p53 is human p53, then the specification would exclude human paralogues of p53, e.g. human p73 and other human genes/proteins of the p53 family. However, it would not exclude paralogues of other species, e.g. p73 from a non-human mammal. Most of the description in El-Deiry refers to p73 generically, and page 4, lines 11-13, teaches as preferred coding sequences ones that encode human p73, and page 15, pages 26-30, describes sequences of p73 orthologues from non-humans that can be used. It does teach using p53 homologues (in this case paralogues) from other species than human.

The Zumstein declaration under 37 CFR 1.132 filed 2/21/06 is insufficient to overcome the rejection of claims based upon El-Deiry for the reasons set forth above. The declaration is given little weight since it presents only the personal opinions of Dr. Zumstein on reading the specification and on the meaning of the term homologue. Also, in ¶ 6, Dr. Zumstein admits that

p73 and p53 share sequence similarity, which is the only required characteristic of homologues, and functional similarity; yet states that in his opinion they are not homologues because there are also structural and functional differences. The differences are why p73 and p53 are paralogues, and not orthologues, but they are still homologues because they share structural similarity. The Office has supplied evidence in the form of two publications that those of skill in the art considered p53 and p73 to be homologues. The issue is NOT whether they are functionally the same protein, but only whether they are homologues as required by the claims, and as defined by the specification.

Response to Brief sections VII.D. 2.&3.

Appellant asserts that El-Diery does not expressly or inherently disclose the limitations of claims 4, 6, 18, 33 and 54. In response, the issues here are basically the same as for the rejections over Clayman, RAC, and Nielsen, and Appellants arguments are not convincing for the same reasons as given above.

Response to Brief section VII.E.

Appellant argues that RAC, as evidenced by Oda and Flaitz, or El Deiry either in view of Zhang fails to render the claimed invention obvious for the same reasons RAC or El Deiry failed to anticipate the claims, discussed above. In response, these arguments have been addressed above.

Appellant asserts for the first time in the brief that there is no suggestion to combine the references. In response, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references

themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the RAC and El Deiry both describe delivery of liquids comprising an adenoviral vector to the mouth, and Zhang taught that when delivering an adenoviral vector the mouth, flavorants can be included. The inclusion of flavorants in oral pharmaceutical compositions is routinely done to improve the palatability of the composition. The brief includes no argument as to why these reasons are not sufficient to suggest the combinations of references cited in the rejection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Scott D. Priebe

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